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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

7590 10/16/2002

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/16/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,178	NAGAI ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-14* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *7-14* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election **without** traverse of Group II (Claims 7 and 12-14) to a method for the treatment of focal cerebral ischemic infarction by administering at least one α_2-antiplasmin neutralizing compound in Paper No. 11 (26 August 2002) is acknowledged. Claims 1-6 are cancelled. Claims 8-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected material, there being no allowable generic or linking claim.

Status of Application, Amendments, and/or Claims

2. The claims amendment of 3 March 2002 (Paper No. 9) has been entered in full. Claims 1-6 are canceled. Claims 8-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 13-14 have been added. Claims 7 and 12-14 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Information Disclosure Statement

4. The information disclosure statement filed 31 August 2001 (Paper No. 6) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it is not present with the application. The information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in

this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1). Applicant is invited to submit a replacement information disclosure statement identical to the information disclosure statement filed 31 August 2001 (Paper No. 6) with the response to this office action for no additional fee.

Specification

5. The Specification is objected to because of the following informalities: brief description of Figure 2 fails to refer to parts A and B. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 7 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods wherein the recited α_2-antiplasmin neutralizing compound is plasmin, does not reasonably provide enablement for mini-plasmin, micro-plasmin, neutralizing compounds with the catalytic domain of plasmin, mutants, and

hybrids thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claim 7 is directed to a method for the treatment of focal cerebral ischemic infarction by administering at least one least one α_2-antiplasmin neutralizing compound. Claim 12 is directed to the method of Claim 7 wherein the compound is plasmin, mini-plasmin, or micro-plasmin. Claim 13 is directed to the method of Claim 7 wherein the α_2-antiplasmin neutralizing compound contains the catalytic domain of plasmin. Claim 14 is directed to the method of Claim 13 wherein the α_2-antiplasmin neutralizing compound contains at least one Kringle domain of plasmin, mutants, and hybrids thereof.

7. The specification teaches that administration of human plasmin to mice with induced focal ischemia can reduce the infarct size.

8. The art teaches that compounds can cover any and all molecules that are organic and inorganic, chemical, pharmaceutical, and biologically derived (e.g. antibodies). The art also teaches that strokes typically are caused by blockages or occlusions of blood vessels to the brain or within the brain. If the occlusion persists for more than five to ten minutes, irreversible damage results. If anticlotting agents reach the clot and blood flow to area is restored, a phenomenon known as reperfusion can occur. Portions of the injured tissue in the penumbra (zone of brain tissue with moderate ischemia and paralyzed neuronal function, which is reversible with restoration of adequate perfusion) can be killed or further injured by the reentry of oxygen or other substances into the area affected by the ischemia. In view of this phenomenon, the extent of tissue damage resulting from ischemia is determined by both the time required to achieve the opening of an occluded vessel and by the series of reactions that follow

as a result of reperfusion and the re-entry of oxygen to the affected tissue. Therefore, simply opening a blocked cerebral vessel will not be sufficient to restore all damage wrought by ischemia nor will it revive dead cells (Eibl et al. EP 0 631 786 B1, pp. 1-3).

9. Thus the claimed invention is a method for the treatment of focal cerebral ischemic infarction by administering plasmin, mini-plasmin, micro-plasmin, a neutralizing compound with at least one Kringle domain of plasmin, mutants, and hybrids thereof, which is not supported by the teachings of the prior art or the instant specification. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Would mutants and hybrids retain the specific biological activities of plasmin; Is a single Kringle domain sufficient to provide the specific biological activity of plasmin?; What compounds can sufficiently replicate the biological effects of plasmin? The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

10. Regarding neutralizing compound, the art recognizes that compound includes a great variety of organic, inorganic, and chemical entities. Due to the large quantity of experimentation necessary to evaluate all the possible compounds with sufficient plasmin-like activity, the lack of direction/guidance presented in the specification what compounds are likely to be active, the absence of working examples directed to non-full length plasmin compounds, the complex nature of the invention, the unpredictability of compound activity (Stedman's Medical Dictionary), and the breadth of the claims which fail to recite limitations for what compounds

exhibit desirable plasmin-like properties, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. Regarding mutants, the art recognizes that compound includes a great variety of plamin-derived entities. Due to the large quantity of experimentation necessary to evaluate all the possible mutants of plasmin with sufficient plasmin-like activity, the lack of direction/guidance presented in the specification what mutants are likely to be active, the absence of working examples directed to plasmin mutants, the complex nature of the invention, the unpredictability of the effects of a mutations on proteins (Rahman et al., 2001), and the breadth of the claims which fail to recite limitations for which mutants might exhibit desirable plasmin-like properties, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

12. Regarding hybrids, the art recognizes that compound includes a great variety of plasmin-derived entities. Due to the large quantity of experimentation necessary to evaluate all the possible hybrids of plasmin and other proteins with sufficient plasmin-like activity, the lack of direction/guidance presented in the specification what hybrids are likely to be active, the absence of working examples directed to plasmin hybrids, the complex nature of the invention, the unpredictability of the effects of a mutations on proteins (Wells, 1990; Ngo et al. 1994), and the breadth of the claims which fail to recite limitations for which hybrids might exhibit desirable plasmin-like properties, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

13. Claims 7 and 12-14 are rejected under 35 U.S.C. 112, second paragraph, because the specification fails to specify to whom or what the recited compounds should be administered. Therefore, the claims are incomplete.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 7 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al (EP 0 631 786 B1). Eibl et al (EP 0 631 786 B1) teaches a method comprising administering plasmin, which meets the limitations of a α_2-antiplasmin neutralizing compound in Claim 7, plasmin in Claim 12, a α_2-antiplasmin neutralizing compound containing the catalytic domain of plasmin in Claim 13, and α_2-antiplasmin neutralizing compound consisting of at least one Kringle domain of plasmin in Claim 14 (pp. 8 col. 14 Claims #24-25). Furthermore Eibl et al (EP 0 631 786 B1) teaches a method of using plasmin to treat a subject at risk for cerebral ischemia and for treatment due to an ischemic event or infarction (pp. 8 col. 14 Claim #25-27). Eibl et al (EP 0 631 786 B1) teaches that ischemia may occur anywhere in the vascular system, the carotid artery bifurcation and the origin of the internal carotid artery are the most frequent sites for thrombotic occlusions of cerebral blood vessels, which results in cerebral ischemia. These instances of ischemia can be localized, or focused in particular areas of the brain as evident from the specific debilitating effects dictated by the location of the ischemia (pp. 2 col. 1-2). In

addition, infarction is defined as a sudden insufficiency of arterial or venous blood supply due to emboli, thrombi, mechanical factors, or pressure that produces a macroscopic area of necrosis; any organ can be affected (Stedman's Medical Dictionary). Hence, the ischemia described by Eibl et al (EP 0 631 786 B1) encompasses focal cerebral ischemic infarction. Therefore, Eibl et al (EP 0 631 786 B1) anticipates Claims 7 and 12-14.

Summary

15. Claims 7 and 12-14 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
October 11th, 2002